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Study Finds Vaccine Delays -- and May Block -- AIDS in Monkeys --- Approach Doesn't Ward Off Virus But Keeps It Under Control; `Partial Protection' Strategy

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By giving a vaccine developed by Merck & Co. an extra boost, Harvard University scientists have prevented laboratory monkeys from getting sick when exposed to a virulent strain of the AIDS virus.

Scientists are heralding the research, published today in the journal Science, as an important advance in the protracted struggle to find a useful AIDS vaccine. The National Institutes of Heath is considering moving the vaccine toward human trials. And Merck, while cautioning against raising false hopes, is racing ahead to conduct safety trials in humans with a similar-acting, second-generation vaccine.

Yet this new vaccine approach raises a host of questions. That is because it works differently than standard vaccines, such as those for smallpox and hepatitis. Most immunizations repel an infectious agent from ever establishing itself. The vaccine tested at Harvard doesn't ward off the virus but rather primes the immune system to control it at very low levels. The vaccinated animals show no sign of illness, whereas almost all the control monkeys given a dummy vaccine became sick or have died.

What's more, because the virus is suppressed to such reduced levels, the chance of spreading the illness is almost certainly much lower. If a similar benefit can be achieved in humans, "that might really change the trajectory of the AIDS epidemic," says Norman Letvin, the scientist at Beth Israel Deaconess Medical Center and Harvard Medical School who supervised the study.

Such a vaccine could pose risks. That's because it would allow some virus to lurk in the bloodstream where it could rise up and cause sickness and death -- a threat that doesn't exist with classical immunizations.

"Will the vaccine delay the disease for 10 or 15 years or prevent it permanently?" asks John Moore, a leading AIDS vaccine researcher at Weill College of Medicine at Cornell University who is familiar with today's study. "No one knows, but given the devastation this disease is causing that would be a nice problem to face."

The sheer scale of the AIDS epidemic -- which has orphaned more than 11 million children in Africa alone and is advancing into Asia and the former Soviet Union -- has pushed researchers to consider a strategy of "partial protection." If researchers could defer the disease, then infected parents might be able to raise their children to adulthood, preventing the mass orphaning that is the hallmark of AIDS in many parts of the world.

But researchers are also being driven by scientific desperation: They are finding it fiendishly difficult to design a vaccine that can induce neutralizing antibodies, the main weapon of most vaccines. Failing that, scientists are looking to vaccines that trigger other parts of the immune system.

Today's study builds on years of work suggesting that antibodies may not be necessary to keep HIV in check. Much of this work was done by Dr. Letvin himself, who in 1982 left a promising career in the lab of a Nobel laureate to study a few monkeys that were dying of a mysterious illness very similar to the then-new disease that was killing homosexual men. A meticulous scientist who plays classical clarinet, Dr. Letvin helped prove that the monkeys had AIDS, and he helped isolate SIV, the simian cousin of HIV.

When many other researchers were focusing on antibodies, which knock out free-floating viruses in the bloodstream, Dr. Letvin concentrated on the immune system's other main arm, killer T-cells, which kill cells the virus has already invaded. Dr. Letvin helped show that this arm alone could keep HIV in check. The vaccine in today's study stimulates killer T-cells but apparently not neutralizing antibodies.

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Dr. Letvin and his colleague Dan Barouch used a so-called naked DNA vaccine that was developed by Merck and consists of two genes from the AIDS virus. Dr. Barouch, the study's primary author, suggested augmenting the vaccine with a special immune-system stimulant called interleukin-2, or IL-2, fused with another immune-enhancing molecule called immunoglobulin. Dr. Letvin didn't think this boosting strategy would work, but he nevertheless gave the go-ahead to Dr. Barouch, a young scientist who conducted much of the research in his spare time while attending Harvard Medical School.

As it turned out, the boost worked splendidly. To test the vaccine, researchers injected the animals with a whopping dose of a "hot" virus, one that causes disease very quickly. The animals that had been immunized with only the naked DNA vaccine did better than the control animals, but half still got sick. By contrast, not one of the eight animals that had been given the vaccine plus IL-2 has developed any signs of disease for eight months. What's more, their immune systems have suppressed the virus to very low, often undetectable, levels.

But even that small amount of virus is worrisome. True, some vaccines for other diseases allow short-lived infections. With polio, for example, the virus infiltrates the body, but paralysis is prevented because the vaccinated immune system kicks in before the virus reaches the central nervous system. Then, crucially, the immune system apparently clears the polio virus from the body.

HIV is a much more formidable opponent because, for reasons that are poorly understood, the immune system cannot completely expel it. Even in patients who suppress the virus to very low levels, HIV can smolder for years and then flare up.

Today's study comes with another caveat: The strain of virus used to test the vaccine -- a hybrid made from human and simian AIDS viruses -- is exactly the same as the strain from which the vaccine is made. "That's not a real-world situation," cautions Dr. Letvin. Indeed, one of the major challenges posed by HIV is its enormous variability.

Nevertheless, Douglas Richman, a prominent AIDS researcher at the University of California at San Diego, says, "It's the first really compelling protection that's been generated without a live-attenuated vaccine," which is a vaccine made from a weakened but still viable AIDS virus. That type of vaccine has protected monkeys far more effectively than any other immunization, but most scientists consider it too dangerous even to test in human beings, because it might cause the very disease it is supposed to protect against.

Today's study uses a vaccine that cannot cause AIDS, but IL-2 is such a powerful immune-system stimulant that it may cause unacceptable side effects. Fortunately, there may be safer strategies that can trigger the same immune response. Dr. Letvin works with several companies, the National Institutes of Health and many academic scientists, and he says, "I know of at least three or four different approaches which I'm not at liberty to discuss but which are attaining the same level of protection" achieved in today's study.

Safety aside, testing a vaccine that doesn't block infection may still prove daunting. HIV can take 10 years to make someone sick, so to know if a vaccine delays disease, clinical trials may have to last that long, or even longer. At the very least, they would take longer than conventional vaccine trials.

Another complication: If subjects in a vaccine trial got infected, would it be ethical to withhold treatment and possibly undermine their future health to see if the vaccine works?

Such ethical dilemmas get supercharged when trials are conducted in the developing world. If subjects there are not offered state-of-the-art treatment, then the accusation may well arise that Western scientists are using Third World citizens as guinea pigs.

Merck declines to comment on these issues, saying it is far too early to know if its vaccine will merit full-scale efficacy trials. What works in monkeys often doesn't work in humans. But the company plans to start small safety trials of the new vaccine. Last year, it commenced similar trials of its first-generation vaccine.

Merck's new vaccine is designed to attain the same results as those in the Harvard study but by a different method. Instead of boosting with IL-2, Merck's new vaccine would piggyback HIV genes onto a harmless virus.

And while the vaccine is primarily designed to protect uninfected people against the disease, it might also be used as an immune-boosting treatment by those already infected with HIV. Clinical trials of the concept with other, older vaccines have already begun.

Inside the company's sprawling research facility near West Point, Pa., Merck's chief of vaccine and antiviral research, Emilio Emini, leans back in his chair and explains the basic concept. "Viruses," he says, "are built by nature" to enter cells and express their genes. "And our immune system," says his colleague John Shiver, "evolved to attack viruses." So by hooking HIV genes onto a harmless virus, Merck hopes to simulate a real infection and so train the immune system to counterattack.

Mr. Emini says the HIV vaccine program has become one of the largest programs in Merck's vaccine division, which accounts for about a quarter of the company's annual R&D expenditures. The research is painstaking. Mr. Emini says the company has tested many monkeys. But now, he says, "we are going heavily into human trials."

Taking a Toll

Global statistics for the HIV/AIDS epidemic for the year ending 1999.

-- People living with HIV/AIDS	34.3 million
-- New HIV infections in 1999	5.4 million
-- Deaths due to HIV/AIDS in 1999	2.8 million
-- Cumulative children orphaned	13.2 million
-- Cumulative number of deaths due to HIV/AIDS	18.8 million

Source: UNAIDS June 2000 report

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